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A CASE OF ACUTE APPENDICITIS ASSOCIATED WITH A PREVIOUSLY UNDIAGNOSED URACHAL CYST

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Being unprepar'd,
Our will became the servant to defect,
Which else should free have wrought.
Macbeth

The acute abdomen is a 'Temple of Surprise', and it has been said that the potential appendicectomist should be prepared to cope with any acute abdominal emergency and should have in his repertoire the knowledge and experience of such major procedures as gastrectomy, cholecystectomy, resection of bowel and hysterectomy.

The following case-report illustrates a further eventuality which may be encountered during appendicectomy. As far as is known, no similar case has been reported in the literature.

CASE REPORT

A young girl, G. v. W., aged 11 years, was admitted to the Transvaal Memorial Hospital for Children on 25 September 1956. The history was one of pain in the right lower abdomen, starting suddenly 24 hours before admission. The pain was stabbing in nature, persistent, and with no area of radiation. The patient had vomited frequently since the onset of the pain and her bowels were regular. She had had no previous attacks of abdominal pain. With regard to micturition, there was no history of difficulty, frequency, burning or haematuria, and she had never been treated for any urinary complaint. The rest of the history was non-contributary.

Examination revealed a well-nourished patient with a flushed face, a temperature of 100° F and a pulse rate of 90 per min.

The pharynx was injected and the tonsils moderately enlarged. The tongue was dry and furred. The rest of the general examination was negative.

The abdomen was well covered with fat and moved poorly on respiration. Marked tenderness and moderate rigidity were felt in the right iliac fossa extending up to the umbilicus and just across the mid-line. There was a suggestion of fullness subumbilically, which was thought to be due to a full bladder. However, the patient stated that she had passed water 'an hour or two ago' and, when offered a bed-pan, was not able to pass water. Psoas and Rovsing's signs were positive and bowel sounds were normal.

A confident diagnosis was made of acute appendicitis, with early spreading peritonitis giving rise to the sub-umbilical tenderness and rigidity.

The operation was performed 1 hour after admission, under general anaesthesia, A right gridiron incision was made, with the skin incision transverse. On separating the internal oblique and transversus muscles, instead of coming onto peritoneum, one encountered the anterior wall of a tense, 'blue-domed', thin-walled cyst (Figs. 1 and 2 indicate the extent of the cyst). When an attempt was made to define the cyst further, it unexpectedly ruptured and out came 150-200 c.c. of urine!

The peritoneum was then opened and a gangrenous, retrocaecal appendix was removed easily in standard fashion. No free fluid or pus was found in the peritoneal cavity. The peritoneum was then closed with plain catgut after a stab drain had been placed down to the pouch of Douglas, since it was thought that some urine might have spilled into the peritoneal cavity.

The skin incision was next extended medially and the wound widened by incising vertically down the lateral border of the rectus sheath and retracting the rectus abdominis medially. The cyst was then traced extra-peritoneally down to the vertex of the bladder, with which it communicated through an opening admitting the tip of the little finger. No communication was noted between the cyst and the umbilicus.

The cyst wall was then cleanly excised and the bladder closed in 2 layers with plain catgut. A drain was placed down to the cave of Retzius through a further stab-incision and the wound then closed in layers with a wound drain down to the internal oblique muscle.

An indwelling urethral catheter was left in to drain the bladder and this drained blood-stained urine for 3 days after the operation. Fluids were given intravenously only for 2 days after operation and the patient received streptomycin and Crystacillin B.D. for 7 days. The catheter and the 3 drains were all removed on the 4th post-operative day and the patient was discharged from hospital 10 days after operation.

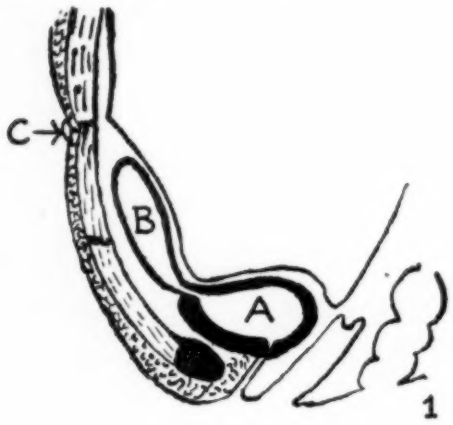
The cyst wall was sent for histological section and the report thereon read as follows:

'The specimen consisted of thin membranous tissue measuring approximately 3 by 1 cm.

'Sections of this specimen show the presence of a vascular connective tissue with a lining that varies from a multi-layered, modified type of pseudo-stratified epithelium to a flattened epithelium, with some parts lined only by a narrow band of very congested fibrous tissue. There is some smooth muscle present but this does not appear to be part of the cyst wall. The cyst wall consists largely of fibrous tissue with an occasional haphazard arrangement of a few smooth muscle bundles. This is not a true

diverticulum of bladder but could be consistent with a urachal cyst or a false diverticulum of bladder.

'The histological features and the age rather favour a urachal cyst than a diverticulum.'



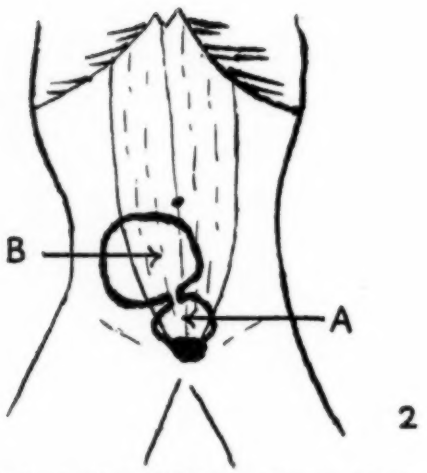


Fig. 1 (above) and *Fig.* 2 (below). Diagrams indicating the extent of the urachal cyst. Fig. 1—sagittal section. Fig. 2—coronal section. A—urinary bladder. B—urachal cyst. C—umbilicus.

DISCUSSION

Kantor (1939)[1] and Carreau and Higgins (1952)[2] review the literature on urachal cysts and deal adequately with their embryology, anatomy and physiology. Urachal cysts are conveniently divided into 4 types:

(i). Those which communicate with the bladder.

(ii). Those which communicate with the umbilicus.

(iii). Those which communicate with the bladder and the umbilicus, forming a vesico-umbilical fistula.

(iv). Those which do not seem to communicate with either.

The cyst mentioned in this case appears to belong to type 1.

Urachal cysts commonly present as abdominal masses and attention is usually drawn to them by recurrent infection occurring in them. They may also present with frequency of micturition or incontinence of urine.

Urachal cysts are notoriously difficult to excise because of adhesions due to recurrent infection, but this cyst-wall stripped particularly easily and no evidence of previous infection was noted.

The possibility that the cyst was, in fact, a simple diverticulum of the bladder has been considered, but one would have expected more smooth muscle in the wall and a continuation of vesical epithelial lining into the diverticular wall. Diverticula arising from the vertex of the bladder do occur in young children and are almost unknown in the absence of obstruction of the bladder outlet, e.g. in a male with posterior urethral valve obstruction or a 'pin-hole' meatus.

The diagnosis of urachal cyst was missed in this case. The diagnosis of appendicitis was quite obvious and the sub-umbilical resistance was thought to be due to spreading peritonitis; frankly, the diagnosis of urachal cyst was never entertained. Percussion of the abdomen was not performed because of the tenderness present and also because it is a test that is so often omitted in a 'classical appendix'—a lesson that I shall not forget easily.

What would have happened if the patient had been catheterized pre-operatively, thus emptying the cyst, can only be surmised. Perhaps the empty cyst might have been unwittingly incised during the opening of the peritoneum, with a resultant unexplained post-operative urinary fistula, or it might have been missed completely with a gridiron incision, to reappear as a mid-line swelling, causing a diagnostic headache for the surgeon at the follow-up clinic.

The reasons for publishing this case are, firstly, to report the very rare association of acute appendicitis and a previously undiagnosed urachal cyst and, secondly, to indicate that many a rude shock may await the too complacent surgeon while he is doing 'the usual appendix'.

SUMMARY

A case in a young girl of acute appendicitis associated with a urachal cyst is presented.

The cyst was discovered unexpectedly during appendicectomy.

This case illustrates a surprise that may await a surgeon while doing 'the usual appendix'.

For permission to publish this case, I am grateful to Mr. W. H. D. Trubshaw and Dr. K. F. Mills, Superintendent, Johannesburg General Hospital.

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EDITORIAL

SURGICAL TREATMENT OF DUODENAL ULCER

Some cases of duodenal ulcer are best left to the surgeon, and many people go further and state frankly that partial gastrectomy is the standard treatment of the condition. There is of course the surgical alternative of gastrojejunostomy, with or without vagotomy. While the benefits of the vagotomy procedure have probably still finally to be assessed, long experience is available of the gastrojejunostomy operation, which was introduced by Moynihan in 1908. In fact, it was through the successful treatment of the commonest complication of this procedure, viz. stomal ulceration, that partial gastrectomy came into vogue. After unchallenged mastery of the field for 2 decades, simple gastrojejunostomy finally gave way in the thirties to partial gastrectomy and, as a general rule, little else is performed for duodenal ulcer nowadays. The universal popularity of partial gastrectomy does not, however, mean that it is of necessity the best treatment or the last word in the matter, and recently an eminent Scottish surgeon, E. L. Farquharson, expressed his 'doubts and misgivings that such an irrevocable and seemingly mutilating operation should be accepted as the standard treatment of duodenal ulcer today'.[1]

Four-fifths of duodenal ulcers are said to be 'cured' by partial gastrectomy, i.e. no long-term complications or alimentary upset are encountered, while 20% of cases suffer various disabilities that Farquharson calls collectively the malabsorption syndrome. In these cases it seems as if the patient merely exchanges his ulcer for postprandial symptoms and nutritional disturbances that are frequently more unpleasant than the ulcer itself. Most are the outcome of the appreciably diminished capacity of the stomach. Restricted intake leads to loss of weight and initial loss of intrinsic factor to anaemia; whilst too rapid emptying causes immediate postprandial symptoms such as bilious vomiting and the dumping syndrome. The term 'intestinal hurry' is no misnomer; in some cases barium reaches the hepatic flexure *within* 5 *minutes* of being swallowed.[2] Defective absorption is therefore bound to occur, causing further alimentary upset, e.g. diarrhoea or steatorrhoea. Since all these complications stem from

VAN DIE REDAKSIE

CHIRURGIESE BEHANDELING VAN DUODENAALSEER

Dit is beter as sommige gevalle van duodenaalseer aan die chirurg oorgelaat word en baie mense gaan nog verder en verklaar onomwonde dat gedeeltelike gastrektomie die standaard behandeling van die toestand is. Daar is natuurlik die chirurgiese alternatief van gastrojejunostomie, met of sonder vagotomie. Terwyl die voordele van die vagotomie prosedure heelwaarskynlik nog finaal bereken moet word, is lang ondervinding met die gastrojejunostomie-operasie, wat in 1908 deur Moynihan ingestel is, beskikbaar. Om die waarheid te sê, is dit deur die suksesvolle behandeling van die mees algemene komplikasie van hierdie prosedure, nl. stomale ulserering, dat gedeeltelike gastrektomie in swang gekom het. Ná onbestrede heerskappy van die veld vir 2 dekades, het eenvoudige gastrojejunostomie finaal in die dertigerjare vir gedeeltelike gastrektomie gewyk en as 'n algemene reël, word selde 'n ander operasie vir duodenaalseer deesdae uitgevoer. Die universele populariteit van gedeeltelike gastrektomie beteken egter nie dat dit noodwendig die beste behandeling of die finale woord in die saak is nie, en onlangs het 'n uitmuntende Skotse chirurg, E. L. Farquharson, sy ‚doubts and misgivings that such an irrevocable and seemingly mutilating operation should be accepted as the standard treatment of duodenal ulcer today'[1] uitgespreek.

Dit word verklaar dat vier-vyfdes van duodenaalsere ‚genees' word deur gedeeltelike gastrektomie, d.i. geen lang-termyn komplikasies of spysverterings-ontsteltenisse word aangetref nie, terwyl 20% van gevalle verskeie gebreke, wat Farquharson gesamentlik die gebrekkige absorberingssindroom noem, ondergaan. By hierdie gevalle skyn dit of die pasiënt slegs sy seer vir na-ete simptome en voedingssteurnisse verruil, wat dikwels meer onaangenaam as die seer self, is. Die meeste hiervan word veroorsaak deur die aansienlik verkleinde kapasiteit van die maag. Beperkte opname lei tot gewigsverlies en die aanvanklike verlies van inwendige faktor lei tot bloedarmoede; terwyl die té vinnige ontleding simptome onmiddellik na ete veroorsaak, soos byvoorbeeld mislike braking en die ophopingssindroom. Die term ‚ingewandshaas' is geen verkeerde benaming nie; by sommige gevalle bereik barium die lewerboog *binne* 5 *minute* ná dit gesluk is.[2] Gebrekkige absorbering sal dus stellig voorkom en verdere spysverteringsontsteltenisse, soos byvoorbeeld diaree of steatoree, veroorsaak. Aangesien al hierdie komplikasies van die afname in die grootte van die maag afstam, is dit natuurlik om voor te stel dat 'n kleiner gedeelte van die maag

the reduction in size of the stomach, it is natural to suggest that a smaller portion of the stomach should be resected. It is generally held, however, that 'inadequate' resection—i.e., removal of less than 70%—is responsible for the 4% of cases in which ulceration recurs. Here Farquharson ventures an observation that may alter the entire approach to the treatment of duodenal ulcer. He states that in some cases of recurrent ulceration after partial gastrectomy observed in Edinburgh, the acid values of the secretion in the gastric remnant were found to be as much as 4 times the normal. If this observation is substantiated, the main purpose of performing a partial gastrectomy disappears.

The second pillar of Farquharson's thesis is this, that the satisfactory treatment of the malabsorption syndrome—i.e. every fifth case submitted to partial gastrectomy—is often impossible. Generally speaking the surgeon carrying out the operation relies upon the 80% chance of cure for his patient. If he fails to achieve it, there is little further that he can do.

Farquharson considers it to be a sad reflection upon present-day medicine that we should have to accept removal of the greater part of the healthy stomach as the best available method of reducing its acid secretion, and he quotes approvingly the remarks of a physician of the thirties: 'If any surgeon wanted to remove four-fifths of my normal stomach to cure a small ulcer of my duodenum, I should run faster than he'!

Is simple gastrojejunostomy the preferable and satisfactory alternative? The present-day objection to the procedure—apart from the often groundless bias in favour of partial gastrectomy—is based upon the liability of gastrojejunostomy to be followed by stomal ulceration. This complication, from casting no more than a shadow over the operation 40 years ago, has grown to be a spectre, and is, Farquharson maintains, 'seriously exaggerated'. The only statistical evidence of its incidence is contained in 5 large series comprising 5,170 cases of gastrojejunostomy performed in the decade preceding 1935. Over follow-up periods of never less than 4 years, only 180 stomal ulcers (3·5%) were recorded. Moreover, 25 years ago the operative mortality from gastrojejunostomy, in common with all major abdominal procedures, was considerably higher than it is today. Tanner, for instance, in 1954, recorded only one death in 107 cases of gastrojejunostomy—a mortality rate lower than that for partial gastrectomy.[3] It seems, therefore, that gastrojejunostomy has lost much of its former terrors. Besides, the surgeon does not burn his boats in performing it, for he can submit the 3·5 cases that subsequently go on to stomal ulceration to partial gastrectomy, which is usually a great success. In theory at any rate, simple gastrojejunostomy seems to be preferable to partial gastrectomy, but prejudice against it remains firm. 'For the unskilled surgeon on the unfit patient, it has much to recommend it', wrote Sir Heneage Ogilvie this year,[4] and in the face of such damning praise in high places it would be a bold surgeon who did not have second thoughts

uitgesny behoort te word. Dit word egter algemeen aanvaar dat ‚onvoldoende' reseksie—d.i. verwydering van minder as 70%—verantwoordelik is vir die 4% van gevalle by wie ulserering hervat. Hier het Farquharson dit gewaag om 'n waarneming uit te spreek wat die algehele benadering tot die behandeling van duodenaalseer mag verander. Hy verklaar dat by sommige gevalle van herhalende ulserering ná gedeeltelike gastrektomie, wat in Edinburg waargeneem is, dit gevind is dat die suurgehaltes van die afskeiding by die oorblywende deel van die maag, so veel soos 4-maal die normale was. As hierdie waarneming gestaaf word, verdwyn die hoofdoel van die uitvoering van 'n gedeeltelike gastrektomie.

Die tweede steunpilaar van Farquharson se stelling is dat die bevredigende behandeling van die gebrekkige absorberingssindroom—d.i. elke vyfde geval wat aan gedeeltelike gastrektomie onderwerp word—dikwels onmoontlik is. In die algemeen gesproke, maak die chirurg, wat die operasie uitvoer, staat op die 80%-kans van genesing vir sy pasiënt. As hy nie hierin slaag nie, is daar weinig verder wat hy kan doen.

Farquharson beskou dit as 'n treurige refleksie op hedendaagse geneeskunde dat, om die suurafskeiding te verminder, ons verwydering van die groter gedeelte van 'n gesonde maag as die bes beskikbare metode moet aanvaar, en hy haal goedkeurend die opmerkings van 'n geneesheer van die dertigerjare aan: ‚If any surgeon wanted to remove four-fifths of my normal stomach to cure a small ulcer of my duodenum, I should run faster than he'!

Is eenvoudige gastrojejunostomie die verkieslike en bevredigende alternatief? Die hedendaagse beswaar teen die metode—afgesien van die dikwels ongegronde vooroordeel ten gunste van gedeeltelike gastrektomie—is gebaseer op die onderhewigheid van gastrojejunostomie om deur stomale ulserering gevolg te word. Waar hierdie komplikasie 40 jaar gelede skaars 'n skaduwee oor die operasie gewerp het, het dit tot 'n spookgestalte gegroei en is dit volgens Farquharson, ‚ernstig oordryf'. Die enigste statistiese bewys van sy voorkoms word gevind in 5 uitgebreide reekse waarby 5,170 gevalle van gastrojejunostomie, wat in die dekade vóór 1935 gedoen is, betrokke was. Gedurende opvolgingsperiodes van nooit meer as 4 jaar nie, is daar slegs 180 stomale sere (3·5%) opgeteken. Bowendien was die operatiewe sterftesyfer weens gastrojejunostomie 25 jaar gelede, in gemeen met alle ernstige maagoperasies, heelwat hoër as wat dit vandag is. Tanner het bv. in 1954 slegs een sterfgeval in 107 gevalle van gastrojejunostomie opgeteken—'n sterftesyfer laer as dié vir gedeeltelike gastrektomie.[3] Dit skyn dus of 'n groot deel van die vrees wat voorheen aan gastrojejunostomie verbonde was, nou nie meer bestaan nie. Buitendien verbrand die dokter, wanneer hy die operasie uitvoer, nie sy brûe nie, aangesien hy die 3·5 van gevalle wat daarna 'n stomale seer vorm, aan gedeeltelike gastrektomie, wat gewoonlik baie suksesvol is, kan onderwerp. In teorie in elk geval, skyn dit of eenvoudige gastrektomie verkieslik is bó gedeeltelike gastrektomie, maar die vooroordeel daarteen bly onwrikbaar. ‚For the unskilled surgeon on the unfit patient, it has much to recommend it', het Sir Heneage Ogilvie hierdie jaar geskryf[4] en met hierdie veroordelende lof van hoë gesag voor oë, sal dit 'n dappere

upon performing a simple gastrojejunostomy. But Farquharson does not relent. We quote the concluding sentence in his paper. 'If I were to develop a duodenal ulcer resistant to medical treatment, such are my misgivings at present about gastrectomy that I think I would try to persuade my old chief to emerge from his retirement, to perform upon me a simple gastrojejunostomy, and to allow me to take my chance of a stomal ulcer.'

1. Farquharson, E. L. (1956): Lancet, **2**, 849.
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dokter wees wat nie na verdere oorweging 'n eenvoudige gastrektomie uitvoer nie. Maar Farquharson gee nie skiet nie. Ons haal die slotsin van sy verhandeling aan: 'If I were to develop a duodenal ulcer resistant to medical treatment, such are my misgivings at present about gastrectomy that I think I would try to persuade my old chief to emerge from his retirement, to perform upon me a simple gastrojejunostomy, and to allow me to take my chance of a stomal ulcer.'

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CARBUTAMIDE AND TOLBUTAMIDE IN DIABETES

Although the existence of the insulin hormone had been known for many years, it was Banting and Best's discovery of means of isolating it from the pancreas of animals that made it possible to use it in the treatment of human diabetes. The discovery revolutionized treatment and completely changed the life and prospects of the victims of the disease, especially in its severer forms. Apart from thyroid therapy, which had been in use for a considerable time before, insulin treatment is the oldest of the hormone therapies. It has enabled many thousands of diabetics to live a normal and happy life and is rightly regarded as one of the triumphs of medicine.

Nevertheless a search continued for other drugs which might be useful in the treatment of diabetes.[1] Perhaps the chief spur to this research was the desire for a medicine which might be taken by the mouth and thus relieve the patient of the burden of daily subcutaneous injection; but certain limitations to the effectiveness of insulin that are evident in some classes of diabetic patient have also provided a stimulus.[1] It is not until recently that any substantial progress has been made in this research. It was noted in 1942 by French observers[2] that the administration of certain sulphonamides resulted in severe hypoglycaemia in animals, associated in some cases with damage to the liver. Other sulphonamides, however, have since been discovered in Germany, which lower the blood sugar but are free from this dangerous toxic action. Two of these stand out prominently, viz. BZ 55 (Boehringer) or carbutamide (Invenol, Nadisan or Orabetic), and D 860 (Hoechst) or tolbutamide (Rastinon, Artosin, Orinase or Dolipol). It appears that these two drugs are alike in their action in diabetes, but that the prolonged use of BZ 55 has in some cases resulted in agranulocytosis,[3] while the use of D 860 has not been accompanied by this side-effect.

Investigations in the use of these two drugs in diabetes therapy have been carried out in Germany and the UK, and in the present issue of the *Journal* (pages 1222 and 1227) articles by Jackson, Linder and others are published reporting clinical trials of BZ 55 (carbutamide, Orabetic) in cases of diabetics admitted to Groote Schuur Hospital, Cape Town, and in the diabetic clinic of the same hospital. At the present time similar trials are proceeding of D 860 (tolbutamide, Rastinon). The Cape Town investigators confirm the results reported elsewhere, particularly (to put it very broadly) that BZ 55 is effective in controlling the hyperglycaemia and glycosuria in 'mild' diabetes (such as that seen in older people) but in the 'severe' form (more often seen in young people) its usefulness is mainly restricted to its action as an adjuvant to insulin therapy. They definitely conclude that the drug represents an advance in diabetes therapy, both in the 'maturity' type of the disease and in the 'severe' type. No toxic effects were observed in the cases treated, but the authors recognize that carbutamide is potentially dangerous and recommend that its use should at present be confined to hospitals where the patient can be kept under adequate observation.

The potential undesirable side-effects of BZ 55 administered over long periods are due to its action as a sulphanilamide (1) in causing blood changes (agranulocytosis), (2) in unfavourably affecting the gastro-intestinal bacterial content, and (3) in its allergic action. The newer product D 860 (tolbutamide, Rastinon) differs from BZ 55 in that the H_2N radicle in the latter is replaced by a H_3C radicle in the former. This molecular difference is held to explain the absence in tolbutamide therapy of the occasional side-effects noted with carbutamide. It has been estimated that throughout the world 35,000 patients have been treated with Rastinon and other brands of D 860, some for a period up to 14 months, and no cases of agranulocytosis have been reported.

As regards the mode of action of these adjuvant drugs in diabetes, it appears that the blood-sugar level is dependent on other factors as well as the quantity of insulin produced by the pancreas. For some time it has been known that there normally exists in the body an enzyme produced in the liver and known as insulinase, which inactivates insulin. Normally a balance is struck between the production of insulin and of insulinase. Diabetes may result from an under-production of insulin (as in the 'young' diabetic) or from an over-production of insulinase (as in the 'elderly' diabetic); and this is thought to be the reason why BZ 55 or D 860 is an effective remedy in the latter type, while by itself it may not control the hyperglycaemia in the former. With these new oral drugs the patient still depends on insulin produced by his pancreas or in-

jected by the physician; and, moreover, the possibility of hypoglycaemia resulting from an overdose, which is a property of insulin, does not exist with the BZ 55 and D 860. There are, of course, other factors concerned in sugar metabolism, and C. H. Best,[4] co-discoverer of insulin has remarked that, apart from their therapeutic possibilities, the study of these new hypoglycaemia-producing substances may disclose valuable information concerning sugar metabolism and its disorders.

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A CLINICAL TRIAL OF CARBUTAMIDE (BZ 55) IN DIABETICS ADMITTED TO HOSPITAL

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While insulin has provided us with a means of combating the acute complications of diabetes, and is able to prevent hyperglycaemia and ketosis for long periods in intelligent and cooperative patients, it is not the complete therapeutic answer to the disease. Even patients who adhere strictly to the diet prescribed and give themselves the correct dose of insulin may develop vascular, ocular, renal, obstetrical and neurological complications. A drawback to the dietary treatment of diabetes is the concession that the average diabetic not infrequently allows himself (perhaps more often herself) the occasional cream bun or slice of cake. The disadvantages inherent in insulin include the difficulty of timing its action to meet physiological requirements, the inconvenience of daily injections, the non-infrequent disfigurement of fat atrophy, and the dangers of hypoglycaemia. An orally administered, non-toxic preparation acting adequately throughout the day and night would be a considerable advance, especially if it could control the brittle severe diabetic as well as the mild.

No preparation of insulin is likely to be effective orally, as this polypeptide is readily digested by intestinal enzymes. Many workers have sought for oral remedies in vegetable and yeast extracts; for example phaseolin[1] had a vogue in Germany, and myrtillin[2] was held to reduce alimentary hyperglycaemia, but even its discoverer could only say that it was feeble and uncertain as compared with insulin. Watanabe,[3] in 1918, showed that guanidine possessed the power of lowering the blood-sugar level, but only when given in poisonous doses. Frank, Nothmann and Wagner[4] found that synthalin (decamethylenediguanidine) retained this reaction on the blood sugar and was much less toxic; they used it on diabetic patients. Graham and Linder[5] participated in a trial organized by the Medical Research Council in 1928; they found that it did have an effect on glycaemia and glycosuria in some patients, but emphasized the frequency and seriousness of the toxic symptoms. The fate of the sugar which disappeared was never solved. Cobalt compounds will destroy the alpha cells of the islets of Langerhans but are too toxic for clinical use. Diethyldithiocarbamate is unreliable clinically.

As long ago as 1942 Janbon *et al.*[6] noted the hypoglycaemic action of a sulphonamide compound, and Loubatières[7] did extensive experimental work with this compound, but it also proved too toxic for human use. In 1955 Frank and Fuchs,[8] Achelis and Hardeback,[9] and Bertram *et al.*,[10] in Germany described the effects of a new sulphonamide derivative, N_1-sulphanilyl-N_2-n-butylcarbamide (BZ 55), both in man and experimental animals. These clinical workers reported that this drug could control most elderly or middle-aged 'mild' diabetics but was without effect in the young 'severe' type. A loading dose of 2½ g. on the first day and 1½ g. on the second were followed by 1 g. daily. A full therapeutic effect was seen within 3 days in many patients but only after 2 weeks in others.

In one series of 82 cases the occurrence of 6 skin eruptions and one case of hepatitis was recorded. The latter was probably unrelated to the drug. In the other series no side-effects were reported. The British workers[11–16] pointed out that many of the German patients were obese and were of the type usually controlled by diet alone in Britain. They felt that the best prospect for BZ 55 was in the treatment of the middle-aged or elderly diabetic (usually over 45 years), who would ordinarily require small doses of insulin in addition to dieting. Their series showed that BZ 55 could be satisfactorily substituted for insulin in about 70% of such cases and that it was relatively ineffective in young severe diabetics or in older diabetics requiring large doses of insulin or showing any tendency to ketosis. The Canadian workers[17] report similar results in smaller series of cases.

CLINICAL TRIAL (IN-PATIENTS)

Messrs. Eli Lilly supplied us with carbutamide (BZ 55) to conduct a clinical trial of this substance at Groote Schuur Hospital. This paper records our findings on

suitable patients admitted to the medical wards over the 4 months, July-October 1956.

Methods

There were 12 cases in this series. Many others were rejected for various reasons. One interesting reason for rejection was the finding that 3 patients remained sugar-free and with normal blood-sugar levels after their insulin had been discontinued.

The accepted 12 were all admitted to hospital either for the control of their diabetes, for the treatment of one or more of its complications, or for a separate illness. Four were seen weekly as out-patients after discharge from the wards. It must be stressed that this trial is one of *short-term* therapy only. Early-morning fasting blood-sugars were estimated daily as far as possible. Capillary and venous blood were taken but only one method of withdrawal was used in any one patient. The blood was taken before insulin or carbutamide was given. The blood sugar estimations were done by Hagedorn's modification of the Hagedorn-Jensen method. Full 24-hour collections of urine were preserved with toluol and the glucose content was measured daily by the method of Somogyi. Those seen as out-patients brought a 24-hour urine with them. The length of the control period depended largely upon the urgency with which beds were required.

The diet was in some cases unrestricted; in others it was low in carbohydrate, accurately estimated and measured by the diet kitchen. In all patients white-cell counts were done before and after and often during the administration of BZ 55. The blood urea, serum protein, thymol turbidity, thymol flocculation or zinc turbidity, and serum cholesterol were estimated before and after treatment. The serum bilirubin and quantitative Van den Berg were frequently measured. Patients were weighed at least once weekly.

Carbutamide was given immediately after breakfast. The routine dosage was 2½ g. on the first day followed by 1½ g. on the second and 1 g. daily thereafter. In some cases doses of 5 g. were given for short periods and in one case 10 g. The method of the change-over from insulin to carbutamide was variable, and is indicated individually in the figures. A relapse usually occurred soon after discontinuing carbutamide, but occasionally a more permanent stabilizing effect appeared to have been produced. Most of the patients could be classified as belonging either to the 'maturity-onset' mild type or 'growth-onset' severe type * of diabetes.

'Maturity-onset' Mild Diabetes

Case 1. J.P.H. (56/06239), European male aged 73 years, weight 159 lb., not obese (Fig. 1). This patient was admitted to hospital because of a left-sided pleural effusion and was then found to be diabetic. He had no 'diabetic complications'. Throughout his stay in hospital he was on a diet containing 127 g. of carbohydrate and as an out-patient he tried to maintain the same diet. Initially he received 15 units of lente insulin per day and was

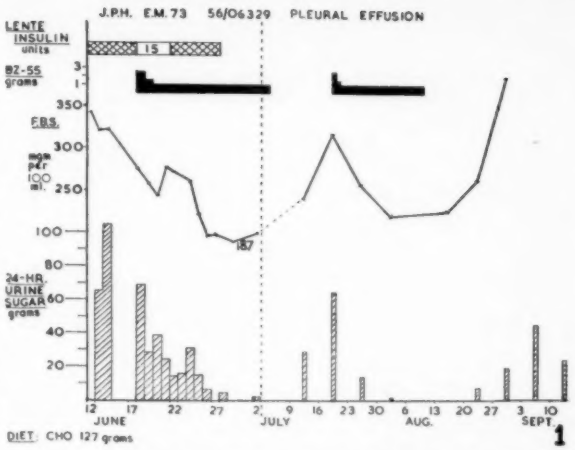

Fig. 1*. Note substantial reduction in blood and urine sugar even when insulin is discontinued. Successive relapses and remissions as BZ 55 is stopped and re-started.

excreting up to 110 g. of glucose with a fasting blood sugar of over 300 mg.%. On carbutamide the fasting blood-sugar fell as low as 187 mg.%. This effect was maintained after insulin was stopped. There was a corresponding considerable fall in the urinary glucose. While he was attending as an out-patient the carbutamide was stopped and the diabetes worsened but again responded to the drug. On stopping it a second time the diabetic state again deteriorated.

Comment. This case clearly demonstrates the efficacy of carbutamide and the necessity for its continuation in an elderly man with recent onset of diabetes.

Case 2. P.L.Z. (56/07076), European male aged 76 years, weight 195 lb. moderately obese (Fig. 2). He was admitted for the operative treatment of a cataract and was discovered to be diabetic. He was not given insulin. On a diet in which the only

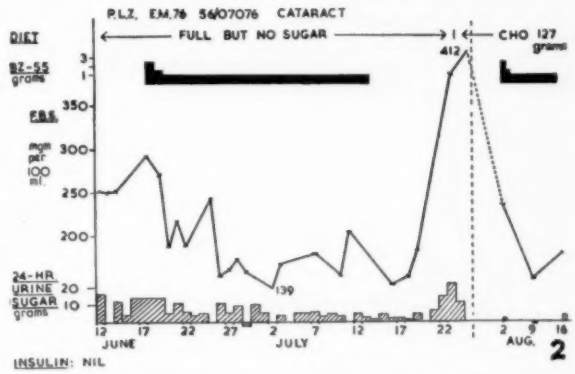

Fig. 2. Note repeated improvement on carbutamide. The urine sugar is lowest on carbutamide plus restricted diet.

* The terms 'growth onset' and 'maturity onset' are used simply to indicate the severe, insulin-sensitive, ketosis-prone, typically young, diabetic and the mild, often obese, typically older, patient respectively. Each variety *may* in fact occur at any age.

* *Note concerning all figures.* EM, AF etc. indicate European male, African female etc. FBS indicates fasting blood-sugar. CHO indicates carbohydrate in diet. Vertical dotted line indicates change from in-patient to out-patient status. Note that the time scale (abscissa) changes at this line. The absence of a block for 24-hour urine sugar indicates that no urine was available on that day; if there was no sugar on analysis this is shown by a small block *below* the base line.

restriction of carbohydrate was the withdrawal of sugar, carbutamide reduced his fasting blood-sugar from over 250 mg.% to as low as 138 mg.%, and his urine sugar also fell. He was severely diabetic 10 days after stopping therapy, improved with a diet containing 127 g. of carbohydrate and further improved by adding carbutamide. He lost 7 lb. weight during his hospital stay.

Case 3. D.F. (56/07253), European male aged 40 years, weight 192 lb. (Fig. 3). He was admitted after a myocardial infarction

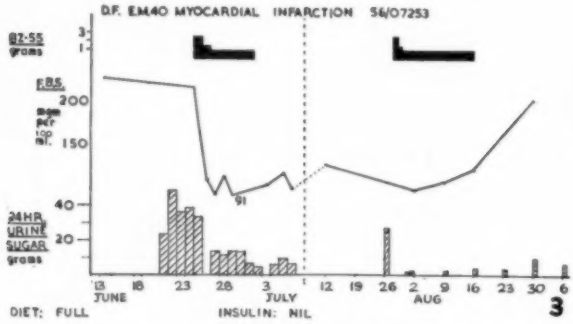

Fig. 3. Again, repeated improvement and relapse on taking and withholding carbutamide on restricted diet.

and was not known to have diabetes before this. His diet remained completely unrestricted. The repeated relapses whenever carbutamide was stopped (6 and 10 weeks after the infarct) indicated that his was not just a 'temporary' diabetic state following on the infarction. He developed a generalized itchy papular eruption while on his second course of carbutamide. This rapidly responded to oral antihistaminic treatment without withdrawal of carbutamide. Insulin was not used. Final weight was 191 lb.

Case 4. E.M. (56/22878), non-obese African male aged 60 years, weighing 152 lb. (Fig. 4). He was admitted with amoebiasis,

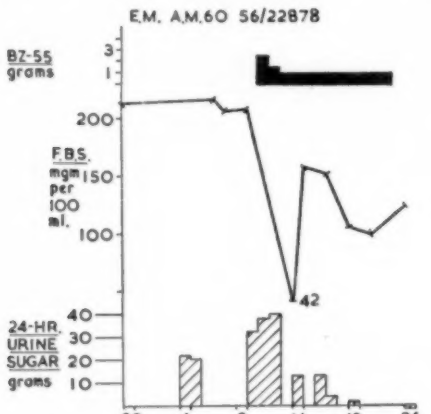

Fig. 4. Good effect of carbutamide. The low fasting blood-sugar was unaccompanied by symptoms.

found to be diabetic, and given carbutamide after he had been adequately treated for the primary disease. He was not a known diabetic and never received insulin. His diet contained 157 g. of carbohydrate per day. Carbutamide halved his fasting blood-sugar and reduced the urinary glucose considerably.

Case 5. G. de V. (55/13547), European female, aged 17 years, weighing 131 lb. (Fig. 5). On an unrestricted diet her mild diabetes

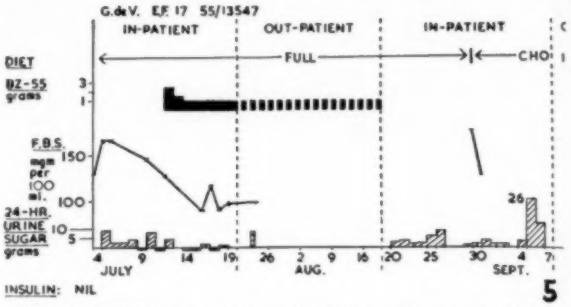

Fig. 5. Control of the diabetes by diet is inferior to that by carbutamide.

was improved by carbutamide, but as an out-patient she took the drug sporadically. On her second admission for a plastic operation of a relatively minor nature her glycosuria increased while off carbutamide, despite restriction of carbohydrate intake. Her sister is also a diabetic of mild type and responded to carbutamide.

'Growth-onset' Severe Diabetes

Case 6. B.R. (182626), lean European male, aged 20 years (Fig. 6). He was admitted for control of diabetes, having been treated with carbohydrate restriction and insulin for 2 years. When his 120 units of lente insulin was replaced by carbutamide his diabetes rapidly deteriorated, thus indicating the failure of this drug to substitute for insulin in his case. When insulin and

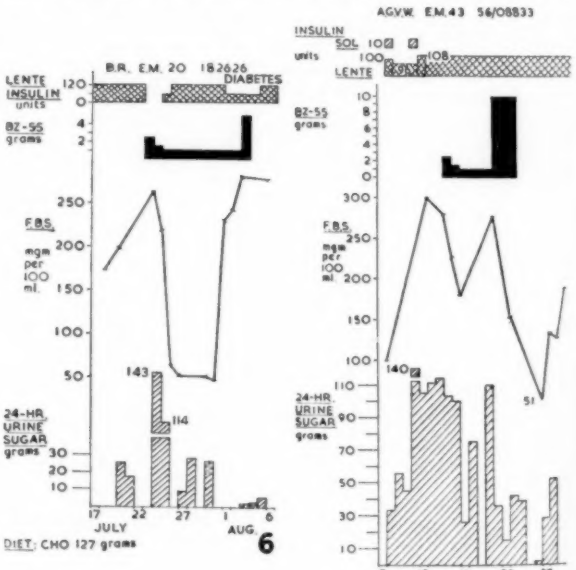

Fig. 6. Sustained morning-hypoglycaemia when BZ 55 was added to his regular dose (120 units) of insulin. One large dose of carbutamide possibly reduced the urine sugar after the insulin had been halved.

Fig. 8. Note distinct effect of very large doses of carbutamide after routine amounts had shown no activity.

carbutamide were given together his fasting blood-sugar fell to very low levels, his urinary glucose fell and he suffered from hypoglycaemic symptoms during the night and early morning. When the insulin dosage was halved and the carbutamide maintained his glycosuria and hyperglycaemia greatly increased. The effect of 5 g. of carbutamide daily was tried; it appeared to be partially successful in reducing these figures.

Case 7. D.G. (56/08338), lean European male aged 10 years (Fig. 7). He was admitted for control of his newly discovered

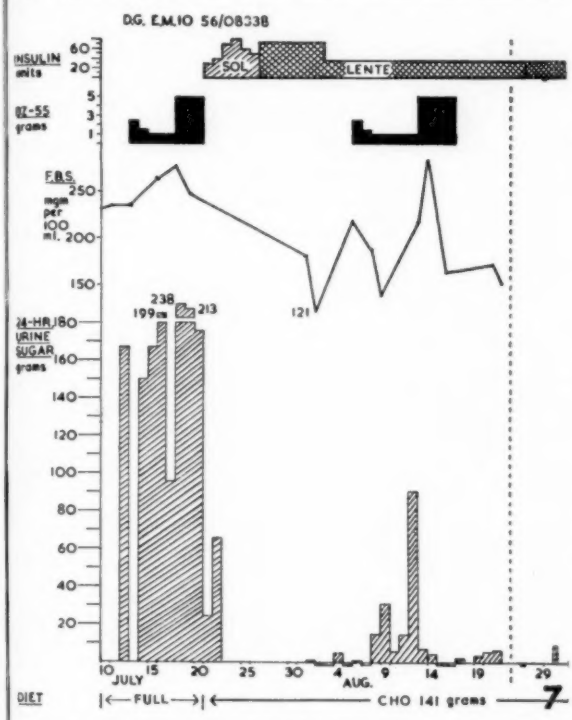

Fig. 7. Ineffectivenes of BZ 55 on its own to control the diabetes. Apparent effect of very large doses acting as an adjuvant to insulin and lowering both blood and urine sugar.

diabetes. On a normal diet he was excreting an enormous amount of glucose daily and his fasting blood-sugar was in the neighbourhood of 250 mg.%. This was completely uninfluenced by the standard dose of carbutamide or even by a dosage of 5 g. a day, maintained for 5 days. The diabetes was then controlled by insulin (60 units daily) and a restricted carbohydrate diet. His insulin dosage was then halved and carbutamide again given in routine dosage. The diabetes relapsed, but an increase of the carbutamide to 5 g. daily now seemed to have some effect. Thereafter he remained well controlled on the smaller dose of insulin without carbutamide. This may or may not have been the effect of the previous administration of carbutamide.

Case 8. A.G.V.W. (56/08833), lean European male aged 43 years. (Fig. 8). A severe diabetic of 2 months duration, he was admitted for control. Large doses of insulin (around 110 units) were unsuccessful. The addition of the standard doses of carbutamide was without effect; increase to 10 g. per day was effective in controlling the diabetes but relapse occurred soon after stopping the drug.

Case 9. N.J. (244204), Coloured female, aged 49 years (Fig. 9). She was poorly controlled on 150 units of lente insulin per day. She had been known to have diabetes for 3 years and had been

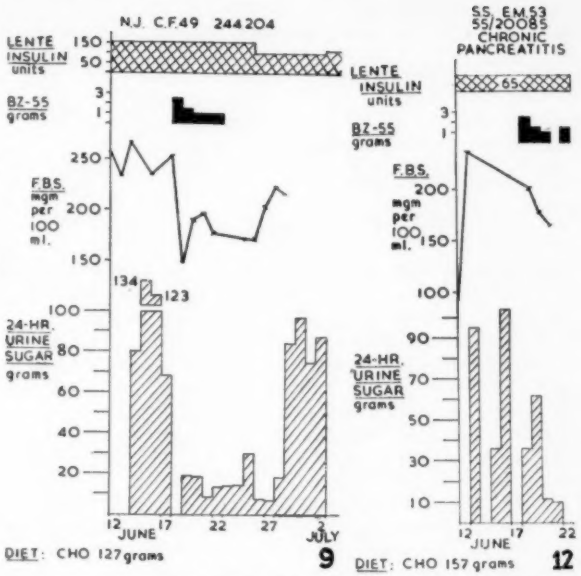

Fig. 9. A distinct effect of standard doses of carbutamide acting as adjuvant to insulin.

Fig. 12. Apparent improvement on carbutamide, with insulin continued.

receiving insulin injections during this period. She weighed 128 lb. With the same dose of insulin, carbutamide in standard amounts appeared to have a good effect, but when the insulin dosage was reduced by a third she relapsed.

Case 10. C.C. (56/14680), Coloured female aged 51 years, weight 146 lb. and slightly obese (Fig. 10). She had been a known diabetic for 5 months before her admission. At first control was

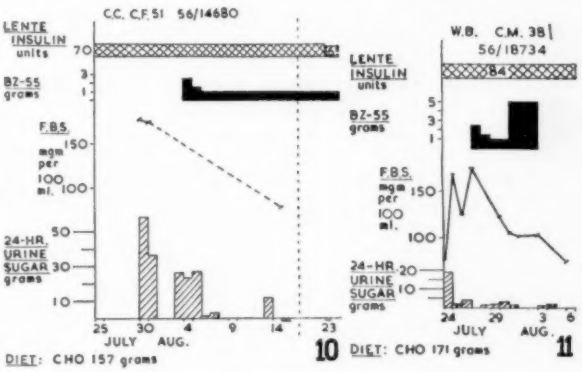

Fig. 10. Control of diabetes improved by standard doses of carbutamide, with previous insulin unchanged.

Fig. 11. Possible improvement of control on carbutamide.

fair with carbohydrate restriction alone but this proved inadequate and she was admitted in mild ketosis after being on small doses of insulin for 2 weeks. Her treatment during the control period was a diet containing 157 g. of carbohydrate and an injection of 70 units of lente insulin a day. Addition of carbutamide in standard doses had a good effect in reducing her glycaemia and glycosuria.

Case 11. W.B. (56/22878), slim Coloured male aged 38 (Fig. 11). He was admitted for control of severe diabetes, which had just been diagnosed. When carbutamide was added to his insulin, improvement seemed to follow, but in the short period of study this appearance may have been fortuitous.

Case 12. S.S., Coloured male, aged 53 years (Fig. 12). He had diabetes secondary to chronic pancreatitis, and appeared to show some response to carbutamide added to his insulin during the short period he was studied.

DISCUSSION

The 'mild' obese diabetic. There is no doubt that carbutamide is effective in controlling the hyperglycaemia and glycosuria in this type of case, as was adequately demonstrated in Germany and has been confirmed by all other workers (e.g. our cases 2 and 3). We strongly agree with the British workers, however, that obesity itself is a serious disorder and should be treated primarily by calorie restriction. Once weight has been satisfactorily lost, control of the diabetes usually ceases to be a problem.

The mild non-obese diabetic. At the present time it seems that this is the type of patient in whom carbutamide (or its successor) will have the greatest value. It will produce steadier control in some, obviate the necessity for insulin injections in some, and allow a less irksome diet in some. The efficacy of carbutamide in this group has been firmly established by other workers and is illustrated by its success in all four patients of this kind that we treated (cases 1, 3, 4 and 5). The Whittington workers[12] found that patients whose fasting blood-sugars were below 275 mg. per 100 ml. were more likely to respond well. Two of our subjects, however, had sugar levels higher than this and their response was excellent. This type of case can be safely dealt with as an out-patient, and is further considered in the following paper.*

Possibility of a free diet while on carbutamide. It is evident from cases 3 and 5 that adequate control of diabetes may be obtained in some instances with complete freedom from dietary control (i.e. allowing sugar, sweets etc. *ad lib.*). This also will be considered further in the next paper.*

The 'severe' diabetic. Another important place for an oral anti-diabetic agent will be as an adjuvant to insulin, producing better control and allowing the use of a single daily injection instead of multiple ones in the more 'brittle' cases, and allowing a reduction in insulin dosage in the others. Less is known of the activity of carbutamide in such cases, although the German authors considered it valueless. For this reason we concentrated particularly on the 'severe' in-patients. Several of these patients were taking very large doses of insulin indeed (see Figs. 6, 8, 9, and 11). We were left in no doubt as to the activity of carbutamide in insulin-requiring cases, although it was quite unable to replace the insulin completely. In fact we were surprised to find evidence of activity of carbutamide in *every* case of severe diabetes, although in 3 instances a very high dosage was needed (*cf.* Kinsell[18]). Certainly one would not dare to continue these doses of carbutamide for long, so that our findings in cases 6, 7, and 8 are, at the moment, of academic interest only.

On the other hand the standard dosage of carbutamide appeared to be effective in assisting control of the diabetes in cases 9 and 10, while in case 6 it actually aggravated the 'brittleness' of the diabetes by producing spikes of severe hypoglycaemia. Further trials of this type of case are needed, since there does seem to be a gleam of hope. Such trials will plainly need to take place in hospital, because of the danger of ketosis if insulin is reduced and of hypoglycaemia if it is not.

Speed of response to carbutamide. Bertram[10] stated that a significant effect might not be obtained until the end of the second week of carbutamide therapy. Our findings were more in keeping with the British workers,[11-16] who observed a response within 12-96 hours. Equally rapid relapse appeared to occur on withholding the drug.

Possible Fallacies

It might be argued that the increased attention paid to patients during the trial made them adhere more strictly to their diets, especially when the carbutamide was actually being given. We do not think this was an important factor in our cases. Some of the British workers used dummy tablets in order to eliminate that factor in their trials.

Secondly it must be admitted that the natural history of diabetes itself is unpredictable, as we found especially when removal of insulin improved diabetic control, or when a patient suddenly became sugar-free for no apparent reason during the control period and was then of necessity omitted from the trial. For this reason the demonstration of repeated remission and relapse of the diabetic state with the use and withdrawal of carbutamide is the clearest way of demonstrating its effectiveness (*vide* case 1).

Toxic Effects

In one patient (case 3) a toxic drug eruption was seen while on his second course of carbutamide. This responded rapidly to oral anti-histaminic therapy in spite of continuance of BZ 55. There were no other side-effects. Nine per cent of the British cases developed rashes, which always resolved when the drug was stopped. We saw no effect on the white-cell count even when very large doses of carbutamide were used. Leucopenia and agranulocytosis is, however, a very real danger, and a fatal case has occurred in the USA, together with another fatality due to a form of allergy.[19] (In our out-patient series there was one case of agranulocytosis.[20]) Duncan *et al.*[11] recorded a definite granulocytopenia in their series as a whole in the initial 2 weeks of treatment, which returned to normal in the majority despite continuance of BZ 55. Six of their 30 patients showed lowered platelet counts. Purpura has also been noted. Headache, malaise and drowsiness has been recorded on high dosage[11] and drug fever has occurred. Kinsell *et al.*[10] reported some depression of radioactive-iodine uptake in the initial period, which returned to normal on maintenance therapy. One patient became mildly hypothyroid after 5 months of carbutamide.[15]

* Page 1227 of the present issue.

Carbutamide may sometimes potentiate the effect of barbiturate and of alcohol, and patients should be warned of this possibility.

In our series, as in others, there was no change in the blood urea, serum protein, thymol turbidity, thymol flocculation, zinc turbidity, serum bilirubin or serum Van den Berg reaction.

SUMMARY

1. A clinical trial of carbutamide in diabetes mellitus was undertaken in the wards on a short-term basis.
2. The claim of other observers that carbutamide is effective in mild diabetes of 'maturity onset' is substantiated. In obese patients dietary restriction remains of primary importance.
3. The possible place of carbutamide (or its successor) in severe diabetes of growth onset is considered. It cannot replace insulin completely but it certainly seems more active in these cases than is usually believed.
4. Toxic effects are potentially serious.

We are indebted to all the physicians and other members of the staff of the hospital who cooperated in this trial.

For references see end of the following paper (page 1230).

A CLINICAL TRIAL OF CARBUTAMIDE (BZ 55) IN THE DIABETIC CLINIC

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From the Diabetic Clinic, Department of Medicine, Groote Schuur Hospital and the University of Cape Town

While the previous paper describes our more detailed observations on a small number of in-patients treated with carbutamide, this one considers the larger number of diabetics treated as out-patients.

Methods

This series comprises 31 patients in all, excluding those who were first investigated in the ward. All but 3 were the 'mild maturity-onset' type of diabetic, who had previously been treated with small doses of insulin or diet only. There were 2 severe diabetics, who were liable to ketosis, and one of intermediate severity.

In general, any insulin which was being used was stopped some weeks before carbutamide was tried. The diet was not usually altered, but in a few cases a more liberal diet was allowed. As far as possible all patients in the trial were seen weekly and had weekly fasting capillary blood-sugar estimations. As well as this, the control was followed by collections of 24-hour urine once a week, by 50 g. oral glucose-tolerance curves before, during and after carbutamide therapy, or simply by qualitative urine-tests. The total white cells were counted before and during therapy, and in many cases the serum cholesterol, blood urea and liver function were estimated before and after 4 weeks of carbutamide.

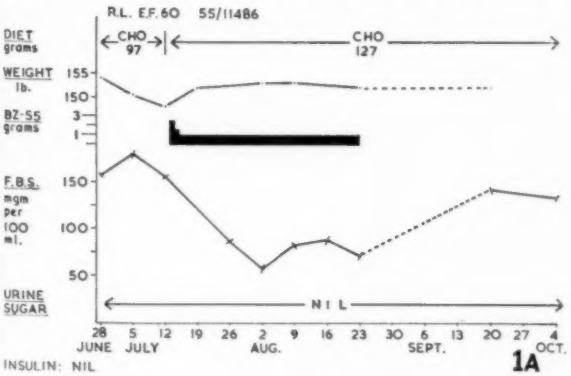

Fig. 1A.* R.L. A non-obese, mild diabetic with high renal threshold. On a larger intake, her fasting sugar gradually diminished with carbutamide, and rose after its discontinuance.

* Conventions regarding figures as in the preceding paper (see footnote on p. 1223, second column). The shaded portion of the glucose-tolerance graphs indicates the abnormal, diabetic zone.

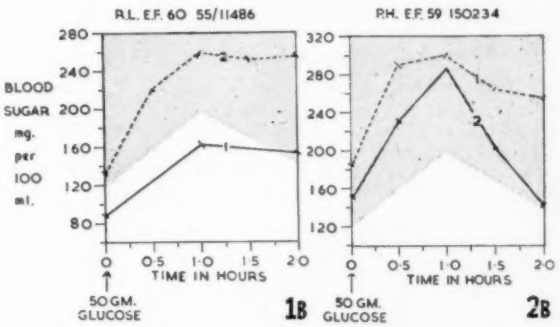

Fig. 1B. R.L., same patient as Fig. 1A. (1) 16 August 1956, on BZ 55 for 5 weeks. (2) 4 October 1956, off BZ 55 for 6 weeks. Her glucose-tolerance curve was far lower while on the drug.

Fig. 2B. P.H., same patient as Fig. 2A. (1) 23 August 1956, 1 week before BZ 55. (2) 2 October 1956, on BZ 55 for 5 weeks. An improvement in the glucose-tolerance curve while under carbutamide is evident, but the tolerance curve is still grossly abnormal.

The dosage of carbutamide was the standard one of $2\frac{1}{2}$ g. the first day, $1\frac{1}{2}$ g. the next day and 1 g. thereafter. The day's ration of tablets were taken all together in

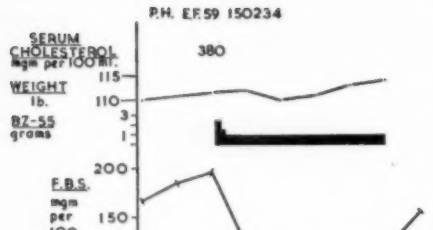

Fig. 2A. P.H. A thin female whose diabetes was of 5 years' duration. We encouraged her to eat everything. The improvement in fasting sugar and urinary sugar while on carbutamide is evident.

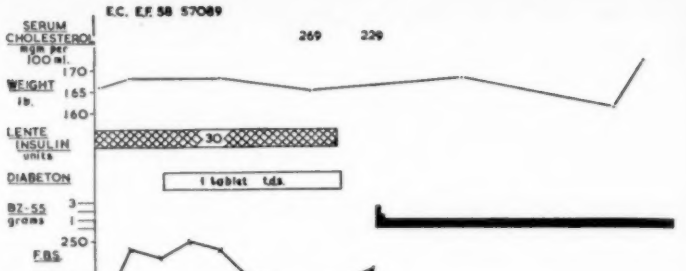

Fig. 3A. E.C. A non-obese diabetic of 5 years' standing, with high renal threshold, in whom oral 'Diabeton'† together with her insulin did not lower the fasting sugar, while carbutamide was effective with no insulin.

the mornings. The 50 g. oral glucose-tolerance tests were performed on patients who had taken a high carbohydrate diet for 1 week; capillary blood was used, and the modified Hagedorn-Jensen method of estimation.

Results

Of the 28 'mild' cases all but 3 showed a distinct response by reduction of blood sugar on repeated occasions together with reduction of urine sugar or improvement of glucose tolerance. In some of the newly diagnosed patients there was also symptomatic improvement of such complaints as pruritus vulvae and loss of energy.

It is not easy to express clearly just how patients responded by giving average or over-all data. For this reason the data from 5 typical mild cases are charted (Figs. 1-5). In order to express a 'mean' response also, the last 3 blood-sugar readings before carbutamide and the first 3 while on the drug in all 28 patients have been averaged. Before carbutamide the mean blood-sugar reading was 182 mg. per 100 ml. (standard deviation=45); while taking this drug it was

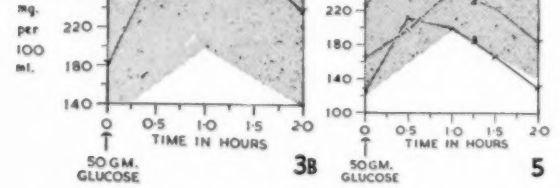

Fig. 3B. E.C., same patient as Fig. 3A. 2 October 1956, after 10 weeks on BZ 55. Notwithstanding the improvement in the fasting sugar while under carbutamide, the single tolerance curve taken during its administration is nevertheless grossly abnormal.

Fig. 5. M.L. An obese diabetic of 1 year's standing. Not on insulin. (1) 12 June 1956, before starting any drug. (2) 13 July 1956, after 1 month on 'Diabeton'. (3) 4 September 1956, after 1 month on BZ 55. There was a distinct improvement of glucose-tolerance on 'Diabeton', but a considerably greater improvement on carbutamide.

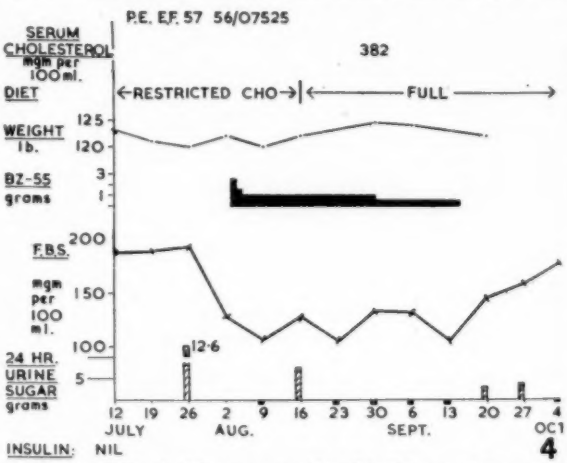

Fig. 4. P.E. A thin woman with mild diabetes of 8 years' standing, who had taken insulin for 6 years. Carbutamide was highly efficacious in lowering the fasting blood-sugar and 24-hour urine-sugar, even in dosage of ½ g. per day.

† 'Diabeton-M' is a proprietary preparation claiming to be extremely effective in controlling all types of diabetes. It contains 5 hydroxyanthranilic acid, vitamin B6, methionine, vitamin C, and a mysterious Japanese extract of 'Morus Bombycio Koidzumi (Moraceae)'. It appears, from our limited observations on this preparation, that it may occasionally have some blood-sugar lowering effect, but not comparable to that of carbutamide.

124 (S.D.=46). The difference between these two means is highly significant ($p=>\cdot001$). At the same time it must be pointed out that a mean figure of 124 signifies that in many individuals the fasting blood-sugar was still too high.

The 3 'mild' diabetics who did not respond at all were not distinguished by any obvious specific characteristics. All were middle aged, one was male, none had had diabetes longer than 10 years, 2 under 3 years. None had outstanding vascular or infective complications.

'Severe' cases. One 'severe' diabetic (R.S.) showed a distinct response to the standard doses of carbutamide, and withstood a withdrawal of insulin (Fig. 6), although the efficacy of the oral drug seemed to wane after a few weeks. The other 'severe' case and the 'intermediate' case showed no response.

Weight. We observed no particular tendency to gain or lose weight on BZ 55. It is well known that overweight patients taken off insulin may, in general, more easily reduce because of the cessation of the appetite-stimulating effect of this hormone. Our patients in this category, however, are too few to allow us to draw any such conclusion from this series.

DISCUSSION

Type of Response to BZ 55

Although 90% of our mild cases showed some response, this is not to say that carbutamide produced perfect control in more than a few. The British workers[11,12] have pointed out that the outstanding effect is on the *fasting* blood-sugar, but that actual glucose-tolerance (i.e. the amount of rise of the blood sugar after ingestion) is not altered. This effect is seen in our tests also (Figs. 2b and 3b).

The speed of response cannot be exactly assessed from weekly visits but in many cases there was a progressive drop in the fasting sugar for a few weeks.

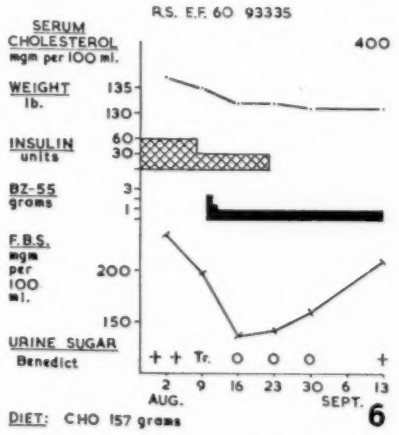

Fig. 6. R.S. A severe non-obese diabetic of 10 years' standing, poorly controlled on 60 units of lente insulin. Better control was obtained with half the dose of insulin, plus carbutamide. After complete withdrawal of insulin, the blood sugar gradually mounted.

We noticed a tendency to *relapse* in some instances, even while the patient was still maintained on the drug, as judged by an increase in the fasting sugar. After the BZ 55 was discontinued the control of the diabetes usually worsened, but not always immediately. There was no instance of the final state being worse than before the treatment. Of course we do not know what might be the result of discontinuing after one or two years' treatment, although reports indicate that sometimes there is a lasting effect.[8-10]

We did not observe a poorer response in patients whose diabetes was long standing, [8-10] nor in those whose initial fasting blood-sugar was over 275 mg.[12]

The 'Free' Diet

In the routine management of diabetes the authors all believe in dietary restriction—in the insulin-requiring case, to allow better control and, in the obese case, to reduce weight. However there are some mild diabetics who are thin or over-thin and who need a fair calorie-intake and a certain amount of insulin to maintain control. If carbutamide (or its successor) can maintain these patients free from glycosuria or hyperglycaemia, without insulin and on an absolutely free diet, there seems no logical reason for any restriction. This we were able to observe in 2 patients whose course is charted (Figs. 2 and 4).

A further young but obese woman of 34 was observed on a completely free diet. Carbutamide reduced her fasting sugar from 300 to 100 mg. per 100 ml. with her weight stationary at 210 lb. The drug was then stopped and a 1,000-calorie diet substituted. Within 4 weeks she had lost 10 lb. and the fasting sugar was maintained at around 155.

The 'Severe' Cases

It is certain that carbutamide cannot be recommended for this type of diabetic. Nevertheless, occasionally it proves to be more effective than would be expected, as in the case depicted in Fig. 6. In 2 further severe cases who were poorly controlled, BZ 55 was added to their insulin and had no evident effect whatever.

Toxic Effects

We observed no effect on the blood urea, liver functions, or serum cholesterol. Two minor rashes were encountered. In only 2 patients were the total white cells depressed below 5,000 per c.mm. One of these women developed total agranulocytosis and became severely ill, as has been already described.[20] We understand, also, that there has been more than one death in the USA from the same toxic effect. Incidentally the lack of ability of BZ 55 to reduce an initially high serum-cholesterol (if this is confirmed) is perhaps a bad omen concerning its efficacy in reducing long-term vascular complications.

CONCLUSIONS

We have no doubt that carbutamide represents an advance in the management of diabetes. Its efficacy in controlling the blood sugar in a high proportion of

diabetics of the 'maturity-onset' type is certain. The control, however, is still not perfect, because of the post-absorptive rise. Furthermore this drug is potentially dangerous, but it is surely the first of a number of substances of which later modifications will have similar or improved anti-diabetic action and less toxicity. The next substance is already with us—D 860 (orinase or rastinon)—in which the amino group is replaced by a methyl radicle. This compound apparently has no anti-bacterial action and appears to be free from danger to the leucocytes.

We therefore strongly recommend that carbutamide (BZ 55) should not at present be used outside a hospital in which special trials are being conducted.

The cost associated with the two foregoing papers was defrayed by grants from the Staff Research Fund of the University, and allied Research Funds. Mrs. J. Smedley, to whom we are indebted for the graphs and for other assistance, is a research assistant under the Council for Scientific and Industrial Research.

All the carbutamide used in these trials was kindly donated by Messrs. Eli Lilly and Company of Indianapolis.

We appreciate the extra work which devolved on the nursing staff and on the technical staff of the department of chemical pathology.

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GRANULOMATOUS ORCHITIS

WITH REPORT OF A CASE

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Granulomatous lesions of the testis are rare. The case to be described is of interest, clinically in that it closely mimicked a testicular neoplasm, and pathologically because of the difficulty in arriving at a definite diagnosis. A provisional rapid section was first considered to show tuberculosis of the testis; on further consideration the histological appearances were regarded as being consistent with sarcoidosis; perusal of the literature finally raised the question of granulomatous orchitis.

The concept of sarcoidosis is still considerably confused and, indeed, there are doubts whether it should be regarded as an entity (Scadding[1]). The histological appearances in this case certainly resemble those of sarcoidosis very closely. However, the fact that the experimental injection of certain acid-fast lipid fractions of human spermatozoa can produce granulomatous lesions very similar to that seen in this case (Berg, 1954[2]), makes one hesitate to apply the label of sarcoidosis without further reservation.

CASE REPORT

C.W.B., a labourer aged 58 years (hospital ref. no. R. I. 207035/55), was admitted to the Churchill Hospital, Oxford, in May 1955, under the care of Mr. A. S. Till. Two months previously he had noticed an aching and a heavy feeling in the left testis. In the course of a few days the testis had become enlarged, and after that, in the patient's opinion, it had varied in size to some extent. There were no other symptoms at all. In the patient's past history there was a story of two operations to his hip at the age of 11 years. The relevant notes were traced, but they gave little information beyond the clinical diagnosis of a tuberculous hip, and that the sinus eventually healed and he was left with a stiff hip.

Examination

The patient looked perfectly well. He was afebrile throughout his stay in hospital. There was no superficial lymphadenopathy. The right testis was normal to palpation. The left testis was about twice the size of the right, smooth and very hard, but retaining its normal shape. Testicular sensation was absent. The epididymis was slightly enlarged, rather hard and nodular, but freely moveable in relation to the body of the testis. The vas deferens was quite normal to palpation.

There was some lack of definition to the right supero-lateral angle of the prostate, but the rest of the gland felt normal. The seminal vesicles were not palpable.

The liver and spleen were not palpable.

There were scars over the left greater trochanter, and the left hip was partially ankylosed.

Investigations

Haemoglobin 97%, 14·4 g. per 100 ml.

White blood-count 4,000 per c. ml. (neutrophils 79%, eosinophils 1%, basophils 1%, monocytes 4%, lymphocytes 15%).

Serum proteins 5·3 per 100 ml. (albumin 3·3 g., globulin 2·0 g.).
Serum acid-phosphatase 4 units.
Blood Wassermann and Kahn reactions negative.
T.B. cultures of 3 early-morning specimens of urine negative.
Mantoux reaction positive with 1/100 old tuberculin.

Radiographs. In the chest old calcified lesions were seen in the left infraclavicular region. No secondary deposits were seen, and no hilar lymphadenopathy. The left hip showed a gross osteo-arthritis with 'the appearances of an old slipped capital femoral epiphysis.' The small bones of the hand showed no cystic changes.

Diagnosis

A neoplasm of the testis, probably a seminoma, seemed to be the most likely diagnosis, in spite of the fact that the epididymis was not quite normal to palpation. The smooth, hard enlargement of the body of the testis, with complete absence of testicular sensation, was quite unlike tuberculosis.

At Operation

The inguinal canal was opened and the cord ligated at the internal inguinal opening. The testis and cord were then removed. The appearance of the testis, after bisecting it in the theatre, did not alter the pre-operative diagnosis of malignant disease of the testis.

Pathological Report

The specimen was reported upon by Dr. W. C. D. Richards as follows (no. 3307/55):

'The specimen consists of a slightly enlarged testis with a portion of spermatic cord. The body of the testis and the epididymis show a diffuse firm, whitish infiltration, but the general shape of the organ is intact.

'*Histology.* A granulomatous lesion affects both the body of the testis and the epididymis (Figs. 1 and 2). In the body (Figs. 1 and 3), except for a few completely atrophied tubules just beneath the tunica albuginea, the supporting cells and the spermatogenic cells of the seminiferous tubules are completely replaced by epithelioid cells and multinucleated giant-cells, which are often arranged so as to resemble tubercles. The outlines of the seminiferous tubules are well maintained, but there is an increase in the reticulin of the basement membrane and of the peritubular interstitial tissues (Fig. 4). The interstitial tissues are infiltrated by lymphocytes and plasma cells, which form a cuff around the granulomatous tubercles.

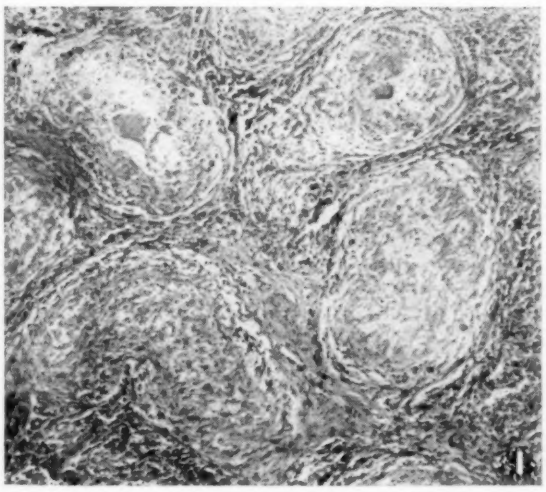

Fig. 1. Low-power view of the body of the testis, showing the tubules to be completely replaced by granulomata consisting of epithelioid cells. Several giant cells are seen. There is no caseation, and appropriately stained sections show no acid-fast bacilli. There is an interstitial infiltration of lymphocytes and plasma cells.

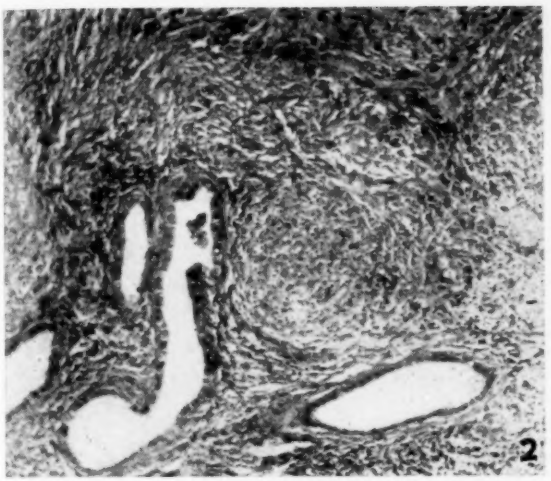

Fig. 2. Low-power view of the epididymis. The granulomatous infiltration is patchy, and more diffuse than in the body of the testis. There is interstitial fibrosis and infiltration by chronic inflammatory cells.

'In the epididymis (Fig. 2) the granulomatous infiltration is patchy, and surrounds degenerating tubules. Some of the tubules contain masses of spermatozoa, around which are macrophages and multinucleated giant cells. Other tubules contain polymorphonuclear leucocytes and macrophages. A few are dilated but free of inflammatory change. There is interstitial fibrosis and infiltration by chronic inflammatory cells but, in contrast to the lesion in the body of the testis, the granulomatous infiltration is more diffuse and, although epithelioid cells are plentiful, giant cells are less numerous. Because of the interstitial character the discrete arrangement of the granulomata observed in the seminiferous tubules is absent.

'Neither in the body of the testis nor in the epididymis is there necrosis or caseation. No micro-organisms can be found in appropriately stained sections. Staining by the method of Berg

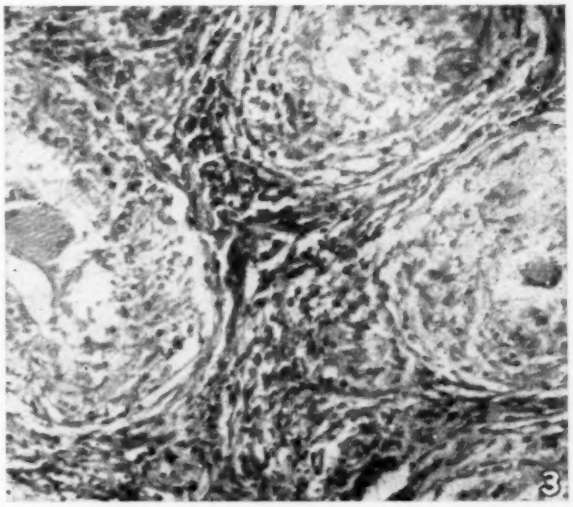

Fig. 3. High-power view of the body of the testis, showing the structure of the granulomata in greater detail.

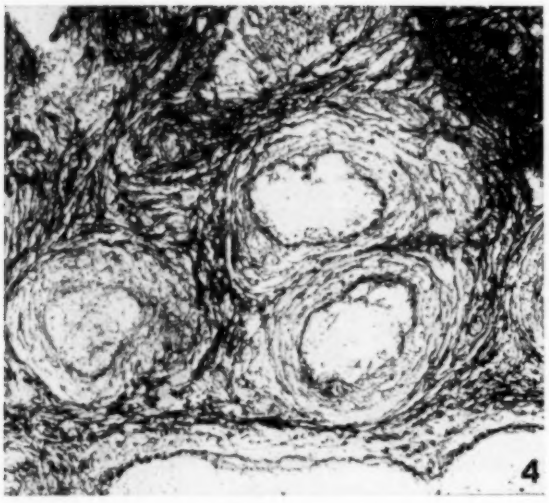

Fig. 4. Reticulin stain of the body of the testis. There is an increase in the reticulin of the basement membrane and of the peritubular interstitial tissue. The strands of reticulin extend into the centre of the granulomata. This is unlike the appearance in tuberculous granulomata, where the reticulin tends to be destroyed.

(1953) fails to reveal spermatozoa or acid-fast material in the body of the testis.

'The appearances are those of a granulomatous orchitis.'

DISCUSSION

The diagnosis in this case would appear to rest between sarcoidosis affecting mainly, if not solely, the testis, and granulomatous orchitis.

For various theories of the aetiology of sarcoidosis reference may be made to the excellent reviews by Cowdell[3] and Longcope and Freiman.[4] The 3 main theories are:

1. That it is a form of atypical tuberculosis.
2. That it is an entity due to a single cause, whether chemical, bacterial or viral, as yet undetermined.
3. That it is merely a tissue reaction to various noxious agents.

Sarcoid-like lesions are known to occur in association with a variety of conditions, including tuberculosis, syphilis, leprosy, leishmaniasis, foreign bodies, and malignant tumours. Chronic exposure to beryllium can give rise to a lesion closely resembling sarcoidosis. It follows that one should exclude all these conditions before diagnosing sarcoidosis. In this case the only condition that needs any serious consideration is tuberculosis, in view of the evidence of tuberculosis in the past both pulmonary and articular. The positive tuberculin reaction is not very signifigant; a considerable proportion of the cases in both Cowdell's and Longcope's series reacted positively.

Most authors have accepted a histological definition of sarcoidosis, in view of the ignorance about its aetiology. According to Longcope and Freiman[4] 'the conclusive demonstration of its presence rests entirely upon the histological structure of the lesions which it produces.' The essential lesions in sarcoidosis are epithelioid granulomata, which are remarkably uniform in appearance, giving a characteristic 'monotony' to the histological pattern. The granulomata do not coalesce. Very characteristic is the absence of caseation and of acid-fast bacilli. In Cowdell's series the rigid application of the latter two diagnostic criteria resulted in the exclusion of no case which in every other way appeared to be sacoidosis. Ricker and Clarke[5] describe the occurrence in 35% of their cases of a fibrinoid necrosis, which is distinguishable from tuberculous caseation, especially by its acellularity. In tuberculous granulomata also the reticulin tends to be destroyed, whereas in sarcoidosis the strands of reticulin can be seen to extend into the centre of the granulomata (Fig. 4). The granulomata may contain giant cells, which however, are not pathognomonic in appearance, and may be of either the foreign-body or Langhans types. Various inclusion bodies in the giant cells, e.g. the Schaumann and asteroid types, have been described in sarcoidosis. They are also found in many other conditions.

Applying the above-mentioned histological criteria, it is apparent how well this case fits the picture of sarcoidosis. One may wonder, however, to what extent the fact that the granulomata are based upon the seminiferous tubules accounts for the regular, 'monotonous' appearance of the granulomata.

Involvement of the testis in generalized sarcoidosis has been described in a few reports, but none is comparable to this case. Nickerson[6] describes one case in which the lesions were few and solitary, and located mainly *in the interstitial tissue*. The liver, spleen and bone-marrow were also involved. Longcope[7] describes a case in a Negro aged 29 years, in which both testis and epididymis were involved, leading to profound changes in the secondary sexual characteristics. Longcope and Freiman[4] mention 2 further cases in a series of 12 autopsies. A search through the literature has revealed no case in which the sole clinical feature was a swelling of the testis.

Apart from the histological criteria, various other investigations may provide supporting evidence in reaching a diagnosis of sarcoidosis, but none offers conclusive proof of the presence of the disease. The tuberculin reaction is frequently negative (60%-70% of Longcope's series) but, as is mentioned above, tuberculin anergy is not an essential requirement for the diagnosis of sarcoidosis. Tuberculin anergy has been used as an argument both for and against the tuberculous theory of the aetiology. There may be an increase in the eosinophils or the monocytes in the peripheral blood, and the ESR may be raised. There may be an increase in the gamma-globulin fraction of the serum proteins. The Nickerson-Kveim reaction, which is the detection, by biopsy, of a sarcoid-like granuloma at the site of intradermal inoculation of a heat-sterilized suspension of human sarcoid tissue, is as yet not of much practical value, for it may take weeks, months, or even a year to obtain a positive result (Longcope and Freiman[4]). The results, however, are

impressive; Siltzbach and Ehrlich[8] record 86% positive results with only 4% false positives.

Consideration of the case presented here thus shows that none of these ancillary methods (the Kveim test was not done) has contributed anything towards establishing the diagnosis.

With regard to the condition described as granulomatous orchitis, the most recent report is that of Spjut and Thorpe,[9] who describe 12 cases. The histological appearances resemble very closely those of the case described here. Small differences are noted. In their series giant cells were seen in only 1 case, whereas they are very numerous in this case. In their series the granulomatous change was in no instance complete. The changes in the epididymis also resemble those in this case; in 5 cases granulomatous lesions were seen which differed from those in the body of the testis in that they were more diffuse and did not have the appearance of being based on the tubular contour; in a further 5 cases there were chronic inflammatory changes but no granulomata.

It is remarkable that Spjut and Thorpe make no mention at all of sarcoidosis in their paper. They do consider the interesting possibility that granulomatous orchitis may be related to the condition known as spermatic granuloma, which occurs in the epididymis.

Spermatic granulomata have been described in several papers (King,[10] Friedman and Garske[11]). Sperm cells, after extravasation into the tissues, disintegrate and liberate an acid-fast lipid fraction, which produces a granulomatous reaction. Berg[2] was able to reproduce this experimentally by extracting this fraction and injecting it subcutaneously into hamsters. The cause of this extravasation is somewhat speculative. Trauma has been invoked as a cause, and cases of injury to the vas have been known to be followed by a spermatic granuloma of the cord (King[10]). Antecedent infection of the epididymis may damage the epithelium, or merely alter the intercellular cement,[10] so permitting the escape of the spermatozoa.

It is difficult to see how this theory can explain the lesion in granulomatous orchitis. Both in this case and in the cases described by Spjut and Thorpe, the granulomata in the body are confined to the tubules. Why should the spermatozoa, on one side only, degenerate *within the tubules* to liberate the lipid fraction which excites the development of the granulomatous reaction. Furthermore, granulomatous reactions are not seen as an aftermath of mumps orchitis, where, in the acute phase, there is extensive breakdown of tubules.

CONCLUSION

It is felt that the case presented is one of granulomatous orchitis. It is evident from the histological sections that the resemblance to sarcoidosis is very close indeed. Points against the diagnosis of sarcoidosis are:

1. The fact that the epididymis does not show quite the characteristic 'monotonous' arrangements of tubercles as seen in the body of the testis, where the appearance may be produced fortuitously by the tubular contours.
2. The fact that, in the few reported cases of testicular involvement in generalized sarcoidosis, there have been significant differences from this case.

On the other hand this case resembles those of Spjut and Thorpe very closely. The only real histological difference is in the number of giant cells observed.

SUMMARY

A case of a granulomatous lesion affecting the testis is described. Clinically it presented as a testicular neoplasm.

The histological appearances of sarcoidosis and granulomatous orchitis are briefly described. It is felt that the most likely diagnosis in this case is granulomatous orchitis, a condition which is being increasingly recognized. The possible relation to spermatic granulomata of the cord is mentioned.

I should like to thank Mr. A. S. Till and Prof. A. H. Robb-Smith for permission to publish this case, and Dr. W. C. D. Richards for advice, and the preparation of the photomicrographs.

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HUNGARY: WORLD APPEAL TO DOCTORS

Dr. Louis H. Bauer, Secretary General of The World Medical Association has announced that he has wired the United Nations urging that body to insist on the admission of all needed aid to Hungary in its present tragic situation.

The 53 national member associations, numbering more than 700,000 doctors, have been urged to send all possible medical and financial aid to the Hungarian people and doctors, through the International Red Cross Committee. The International Red Cross was notified that these steps had been taken. The text of these telegrams read:

'Mr. Dag Hammersjold, United Nations, New York, New York. As Secretary General of the World Medical Association, representing more than 700,000 doctors of the world, I strongly urge that the United Nations insist that the International Committee of the Red Cross be permitted to distribute without interference all necessary aid to the devastated people of Hungary. I also urge that every necessary step be taken to prevent further butchery, and deportation of Hungarian citizens and that the actions of those responsible for these atrocities be strongly condemned by the General Assembly, in accordance with the general purposes of the United Nations.—Louis H. Bauer, M.D.'

'President International Committee of the Red Cross Geneva, Switzerland. Today have urged all national member associations and their membership to send all possible aid to Hungary through your organization. Have also urged United Nations to facilitate your distribution of aid without interference.—Louis H. Bauer, M.D., Secretary General. The World Medical Association.'

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

The following received higher degrees and postgraduate diplomas at the Graduation Ceremony of the University of the Witwatersrand on 14 December 1956:

Doctor of Medicine
P. Barkhan
D. Newby

Master of Surgery
R. W. G. Stuart

Diploma in Medicine
M. J. Goldberg
J. Schneider
N. Segel

Diploma in Obstetrics and Gynaecology
Y. R. J. Dugas
D. Silove
A. J. L. van Rooyen

Diploma in Clinical Pathology
H. W. Alberts

Diploma in Psychological Medicine
A. P. Burger
T. E. Lynch
A. Moffson
E. W. Rayner
A. J. van Wyk

Diploma in Public Health
B. L. Ross
H. N. v. d. G. Gertenbach
H. S. Hurwitz
W. H. G. Kuschke
I. W. F. Spencer

Sixth Professional Examination for the Degree of M.B., B.Ch. The following candidates have completed all the requirements of the Sixth Professional Examination for the degree of M.B., B.Ch.:

Abroms, I. F.
Amoils, S. P.
Andrew, W. K.
Apostolis, C. G.
Aron, P. L.
Bakst, C. M.
Bannink, A.
Baumslag, N.
Beardall, P. J.
Berge, J. E.
Blackstone, I. W.
Broer, I. H.
Brownstein, E. G.
Buchanan, A. J.
Carpel, C. L.
Chissick, G.
Clennar, C. B.
Cooper, B. C.
Docrat, A. K.
Esrock, B.
Fainman, L. N.
Fisher, E. M.
Gcabashe, V. M.
Gladstone, L. Z.
Greenstein, A. J.
Gutowitz, H. E.
Hoffmann, D. A.
Jacobson, I.
Jaffe, N.
Javett, S. L.
Jersky, J.
Kannemeyer, A. H. R.
Kara, I. M.
Katz, J.
Katz, J. S.
Katzen, N. G.
Kavin, H.
Keogan, P. G.
Khan, M.
Koopowitz, J. I.
Lautenbach, E. E. G.
Leeb, J.
Levin, J.
Levin, N. W.
Lew, W. H.
Louis, S.
Lurie, S. D.
Mashalaba, N. N.
Miller, J. D. R.
Myer, E. C.
Naidoo, G. V. D.
Nichol, D. A.
Parirenyatwa, T. S.
Paterson, R. S.
Popper, S.
Prowse, C. M.
Rabinowitz, D.
Rogers, N. M. A.
Rummel, S. P.
Sacks, J.
Sarantos, T. C.
Seedat, M. I.
Segal, E. B.
Sevel, D.
Shapiro, S.
Slasky, B. S.
Sonnabend, J. A.
Sonnendecker, E. W. W.
Sorokin, M.
Stevens, K.
Walker, J. D.
Welch, J. D.
Wright, J. N. D.
Yodaiken, R. E.

UNIVERSITY OF CAPE TOWN

The following degrees were conferred at the Graduation Day Ceremony at the University of Cape Town on Friday, 14 December 1956

M.D.

J. S. du T. de Wet: Subject of Thesis: 'Evaluation of a common method of convulsion therapy in Bantu Schizophrenics'.

A. Kipps: Subject of Thesis: 'A study of the soluble antigen of the bluetongue viruses'.

D. H. Shennan: Subject of Thesis: 'Tuberculosis in the Bantu of Southern Rhodesia'.

Miss J. J. Walker. Subject of Thesis: 'Skin and Tuberculosis'.

M.B., Ch.B.

G. C. Adams
T. G. Ashworth
M.A. Aucamp
N. M. Baker *
A. Barmania
Miss R. F. Barsky
I. R. Becker
B. L. Belonsky
Miss M. R. Benjamin
Miss M. Berger
Miss G. L. Bracken
I. Bruk
J. Budow
G. D. Burger
Gerhardus D Burger
E. J. R. Caney
G. J. A. Currie
H. P. du Plessis
Miss J. M. E. du Plessis †
J. A. du Toit
M. M. S. du Toit;
D. J. G. Fergusson
M. J. Fisher
Miss R. Friedman
S. A. Gamiet
I. M. Gans ††
R. L. George
F. C. Glaum
A. Groll
C. W. H. Harrison
Miss K. E. Haupt
J. J. Heydenrych
Miss W. B. Humphreys
J. Jacobson
M. Jacobson
E. Kabrun
E. Kahn
Miss J. D. L. Kane-Berman
S. Katz
J. R. Keet
J. D. King
L. H. Krut
L. A. S. Lemmer
A. M. Louw
C. J. Louw ††
A. F. Malan
W. D. Marais
J. H. Marcus
I. M. Marks
Issy Myers
J. L. W. T. te W. Naudé
P. B. Neame *
J. J. Nel *
R. Nilssen
H. Pogrund
K. L. Polson
J. E. P. van Loon
D. J. Pudifin
D. C. Rayner
J. R. Reuben
A. W. F. Richey
H. E. Rust
B. I. Sacks
M. E. Samols ¶
J. R. Saunders
Miss M. Sender
P. Shrock
A. P. Simpson
B. Singer
O. W. Smyth
K. B. Sundgren
S. W. van der Merwe
J. O. T. van Helsdingen
M. D. Vellema
P. L. Vogel
G. J. von Wielligh
E. Vosloo
J. J. Waugh
Miss A. G. Wesley
G. P. Wilson
J. G. Wyatt
J. M. Wynne ††

Diploma in Nursing

Miss E. W. Jones

* Distinction in first professional examination.
† Distinction in second professional examination and degree with second-class honours.

M. Med. (Anaes.): N. W. Schmaman.

M. Med. (Pathology): C. P. Retief.

M.O. & G.: H. V. F. Jordaan.

Ch.M.: R. B. Kihn.

Diploma in Public Health. J. H. Dreyer, P. A. Lückhoff, S. L. Skoll, L. S. Smith, M. G. van Schalkwyk, L. B. Wilms.

†† Distinction in second professional examination.
¶ Distinction in first professional examination and degree with second-class honours.

ANTICOAGULANTS AND CHOLESTEROL-INDUCED ATHEROMA

At a meeting of the Research Forum, University of Cape Town, held at Groote Schuur Hospital on 4 December 1956, a paper by Dr. C. Merskey, Prof. N. Sapeika, Dr. C. J. Uys and Dr. B. Bronte Stewart was read by Dr. C. Merskey on the following subject:

(*a*) The effect of anticoagulants and fats (both saturated and unsaturated) on cholesterol-induced atheroma in rabbits.

(*b*) Abnormal bleeding diathesis produced in cholesterol-fed rabbits.

(*a*) In the first series of experiments rabbits were given cholesterol with and without the anticoagulant drug phenindione. Rabbits fed with phenindione and cholesterol developed more atheroma than those not given phenindione. In the next experiments rabbits were given either cholesterol alone or cholesterol with a saturated or an unsaturated fat. The mean serum-cholesterol levels were higher and the degree of organ cholesterolosis greater in animals given either variety of fat with cholesterol than in rabbits given cholesterol without fat. The serum-cholesterol levels were higher in the animals given unsaturated fat with cholesterol than in those fed with saturated fat and cholesterol.

(*b*) A prolonged coagulation-time and increase in residual serum-prothrombin was noted in the cholesterol-fed animals even when phenindione was not given. These coagulation anomalies developed as the serum-cholesterol rose. Analysis of this defect showed the possible presence of an anticoagulant in the rabbit plasma. Increasing proportions of blood from affected rabbits mixed with blood from normal rabbits caused prolongation of the coagulation time and increased amounts of residual serum-prothrombin in the normal rabbit's blood. There appeared to be excessive amounts of prothrombin and factor VII in the plasma of affected animals. Blood-thromboplastin generation was defective, the defect lying in the serum fraction. This could be fully corrected by normal or haemophilic serum, partially corrected by the serum of patients on phenindione therapy, and not at all by the serum of patients with Christmas disease. Two patients with nephrotic syndrome and levels of serum cholesterol over 1,500 mg. per 100 ml. showed a prolonged coagulation time and defective blood-thromboplastin generation.

ASSOCIATION NEWS : VERENIGINGSNUUS

MEDICAL PROTECTION

At the last meeting of Federal Council it was agreed that the Medical Association of South Africa would conclude an arrangement with the Medical Protection Society Ltd., of London, whereby the Society would form a South African Branch in conjunction with the Association.

Protection has been afforded to our members for many years by an arrangement with the Atlas Assurance Company, who have rendered a valuable service to the medical profession in this country by the cover they have provided. Cordial relationships have existed and do exist between the company and the Association, and the arrangement now reached with the Medical Protection Society provides an alternative service to members but does not supersede that which the Atlas Company has provided all these years.

A memorandum explaining the service of the Medical Protection Society has been posted to all members of the Association for their consideration, and it is for the member to decide on the form of protection which he wishes to have. One thing is certain, however, and that is that every medical practitioner should be protected in one way or the other. Neglect to make this provision is folly, as is also failure to see that the protection is adequate in respect of the amount of the indemnity.

It has been found that the previous lower limit of £1,000 is no longer a reasonable or adequate cover, and this has now been raised to £2,000. Some forms of practice require protection against much larger claims.

The forms which have been circulated include an application form, and the commencing date for cover by the Medical Protection Society is the date on which the completed form is received at the office of the Secretary of the Medical Association of South Africa, P.O. Box 643, Cape Town. Members who may decide to change their protection from some other company or society should indicate when the next renewal premium would normally fall due.

PASSING EVENTS : IN DIE VERBYGAAN

Mr. Alec Singer, M.Ch. Orth (L'pool) and *Mr. Martin Singer*, F.R.C.S. are changing their consulting rooms to 909 Norwich House, Heerengracht, Cape Town, as from 1 January 1957. Their new telephone numbers will be 2-7712 and 3-2833.

* * *

Union Department of Health Bulletin. Report for the 7 days ended 29 November 1956.

Plague, Smallpox: Nil.

Typhus Fever: No further cases have been reported from the Uitenhage district since the notification of 8 November 1956. This area may now be regarded as free from infection. One (1) native case in the Graaff Reinet Native location. Diagnosis based on clinical grounds only.

Epidemic Diseases in Other Countries.

Plague: Nil.

Cholera in Calcutta (India); Chalna, Chittagong, Dacca (Pakistan).

Smallpox in Ahmedabad, Bombay, Calcutta, Cuddalore, Jodhpur, Karikal, Madras (India); Makassar (Indonesia); Baghdad, Basra, Margil, Mosul (Iraq); Dacca (Pakistan); Saigon-Cholon (Viêt-Nam); Mombasa (Kenya); Dar es Salaam (Tanganyika).

Typhus Fever: Nil.

Union Department of Health Bulletin. Report for the 7 days ended 6 December 1956.

Plague, Smallpox, Typhus Fever: Nil.

At date of latest information there existed:

Plague: Nil.

Cholera in Chittagong, Dacca (Pakistan).

Smallpox in Ahmedabad, Allahabad, Bombay, Calcutta, Delhi, Jodhpur, Madras, Visakhapatnam (India); Baghdad, Basra, Margil, Mosul (Iraq); Karachi (Pakistan); Nairobi (Kenya).

Typhus Fever in Baghdad (Iraq); Alexandria (Egypt).

* * *

Lady Whitby and family desire to express their warmest thanks to the many friends and colleagues of the late Sir Lionel Whitby who so kindly sent messages of sympathy and condolence in the loss they have sustained.

* * *

Anaesthetics. Williams and Wilkins Company of Baltimore, U.S.A., will begin publishing in February 1957 a bi-monthly journal under the title 'Survey of Anesthesiology'. It will carry paraphrased digests of articles along with appended editorial comments.

Refresher Course, University of Natal. A refresher course for general practitioners will be held at the Medical School, Durban, from 29 April to 3 May 1957, consisting of lectures and demonstrations illustrated by clinics and ward-rounds of various hospitals in Durban. The fee for the course if £5 5s. 0d. and applications should reach the Secretary to the Refresher Courses Sub-Committee Department of Gynaecology and Obstetrics, Faculty of Medicine, Medical School, University of Natal, Durban, on or before 31 March 1957.

REVIEWS OF BOOKS : BOEKRESENSIES

PRIMARY PSYCHIATRIC SYNDROMES

The Primary Psychiatric Syndromes. Criteria for Clinical Diagnosis. By Dwight L. Moody, L.R.C.P., L.R.C.S. (Edin.), L.R.F.P.S. (Glasg.), D.P.M. Pp. xiv + 356. 37s. 6d. post Is. 3d. Bristol: John Wright & Sons Ltd. 1956.

Contents: I. Introduction. II. Classification. *Part I.—Reactive Conditions.* III. Reactive Disturbances. IV. Fear States: Reactive Anxiety. *Part II.—The Psychoneuroses.* V. Fear States: Anxiety Neuroses. VI. Fear States: Conversion Hysteria. VII. Seizure Syndromes. VIII. Fear States: Phobiae. IX. Fear States: Mixed Neurotic States. X. The Neurasthenias. XI. Hypochondria. XII. Behaviour Disorders. XIII. Approach to Diagnosis of Psychiatric Syndromes as Exemplified by Sociopathia. *Part III.—The Psychoses.* XIV. The Maniacal States. XV. Manic-depressive Psychosis. XVI. Chronic Hallucinatory Psychosis. XVII. Melancholia. XVIII. The Schizophreniae. XIX. Paraphrenia. XX. The Paranoiae. Part IV.—Personality Behaviour Patterns. XXII. Hypomanic and Melancholic Reactions. XXIII. The Paranoid Personality. XXIV. Schizothymic and Schizoid Reactions. XXV. Electroencephalography in Diagnosis. XXVI. Summary and Suggestions. Bibliography. Index.

This volume may be found to meet the needs of the clinician (but more especially of the student) for a presentation of the patterns of mental illness on a strictly clinical basis.

The lay-out of the book is such as to make it usable for quick reference (it is almost in the form of condensed notes) in the appraisal of a case, and it may prove of value to the student in avoiding the prevailing bewilderment which seems often to attend his first approach to psychiatry. A.B.

MENTAL HEALTH

The Approach to Mental Health. By David T. Maclay, M.D., D.P.M. Pp. 144. 12s. 6d. London: Thorsons Publishers Ltd. 1956.

Contents: Preface. Introduction. I. The Instincts. II. Purposeful Aspects of Mental Life. III. The Unconscious Mind. IV. Mental Mechanisms: Personality. V. The Child at Home. VI. Social Aspects of Psychology. VII. How Nervousness is Treated. Index.

This is a book specially written for the 'educated layman' by a psychiatrist. The author calls upon his clinical experience to illustrate the various factors which contribute to 'normality' and thus to normal human relations. He is enlightening on the wide variations within what is normal.

The first four chapters present a brief introduction to psychology. These are followed by valuable chapters on The Child at Home and The Treatment of Nervousness etc.

A.B.

PSYCHOTHERAPY

Dynamics of Psychotherapy—The Psychology of Personality Change. Volume I. Principles. By Percival M. Symonds, Ph.D. Pp. xi + 211. $5.50. New York and London: Grune & Stratton, Inc. 1956.

Contents: Preface. I. Introduction. II. Process of Psychotherapy. III. Indications for Counseling. IV. Indications for Psychotherapy. V. Contraindications for Psychotherapy. VI. Nature and Definition of Psychoneurosis. VII. Dynamics of Psychoneurosis—1. VIII. Dynamics of Psychoneurosis—2. IX. Neurotic Trends and the Neurotic Symptom. X. Predisposing and Precipitating Factors in Psychoneurosis. XI. Goals of Psychotherapy—1. XII. Goals of Psychotherapy—2. XIII. Goals of Psychotherapy—3. XIV. Spontaneous Recovery from Psychoneurosis—1. XV. Spontaneous Recovery from Psychoneurosis—2. XVI. Some Theoretical Issues. Bibliography. Index.

In these days in which we have seen the triumph, but also the abuse, of so many (admittedly useful) physical methods of treatment in psychiatry, it is pleasant and reassuring to come across a work which deals exclusively with the principles and dynamics of (objective) psychotherapy. After all, a psychiatrist's main job still remains to find out 'whether there is something on a man's mind'. It is a sad reflection on present-day psychiatric practice that the terms 'shock treatment' and 'psychiatry' have come to mean the same thing to the layman.

In writing this book it was the intention of the author to spell out with considerable detail the basic principles of psychotherapy, its processes and procedures. He has gathered together much material that is now only available when passed on by word of mouth in seminars or in technical reports widely scattered in periodicals and books.

A special chapter is devoted to counselling and the indications for counselling, which will make the book of interest not only to psychiatrists, but also to social workers and clinical psychologists.

A.B.

CORRESPONDENCE : BRIEWERUBRIEK

STUPOR IN INFANTS AFTER NASAL DROPS

To the Editor: In your issue of 3 November 1956, Walt and Savage[1] report a case of stupor in a premature infant aged 5 weeks, who was given at least 10 drops of Tyzine hydrochloride nose drops (0·025%), at approximately 4-hourly intervals over a period of 16 hours. This infant weighed 4 lb. 1 oz. at 4 weeks, i.e., 1 week before the medication for a 'cold' with 'blocked nose'.

The authors consider that the infant was probably given more than 10 drops. This is extremely likely, as is borne out by the experience of Brainerd and Olmsted who 'were impressed with the difficulty of administering an exact number of drops owing to the extremely high surface-tension of the solution'. 'It would thus not be difficult for a parent to unknowingly administer an excessive amount of the drug. . . .' Fabricant has also emphasized that the absorption is 'maybe much greater in the presence of inflamed membranes . . .'[2]

Drowsiness in young infants after the administration of the pressor amines is well recognized and has been considered as due either to hypersensitivity or to overdosage. 'Age and/or the size of the infant is an important factor in determining whether or not drowsiness may occur. The majority of infants who exhibited drowsiness of a severe degree were under the age of 6 months'.[2]

These views clearly have even greater force when it is appreciated that the case reported by Walt and Savage involved a premature baby, and that the dosage administered was probably far in excess of that recommended by the manufacturers.

We agree that the use of the pressor amines should be attended with caution in the very young, and advise against the use of the stronger solution (0·1%) in infants and children under 6 years. An intranasal solution of 0·5% (which can be further diluted) is available for infants and a calibrated dropper (marked to indicate 1 and 2 drops) is provided to guide parents or other inexperienced persons. This product is called Tyzine Pediatric Drops and is also distinguishable from the stronger product by its pink colour. This should prevent overdosage accidents of the kind described by Walt and Savage.

B. E. Bratt, M.P.S.
Pfizer Laboratories S.A. (Pty.) Ltd.
P.O. Box 7324
Johannesburg
6 December 1956

1. Walt, F. and Savage, L. (1956): S. Afr. Med. J., **30**, 1064.
2. Brainerd, W. K. and Olmsted, R. W. (1956): J. Pediat., **48**, 157.